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WO 02/19994 A2

(54) Title: THE TREATMENT OF INFLAMMATORY DISORDERS

(57) Abstract: A method of treating an inflammatory disease or an autoimmune disease in a subject, comprises the administration of mefloquine.

THE TREATMENT OF INFLAMMATORY DISORDERS

Field of the Invention

This invention relates to the treatment of inflammatory disorders.

Background of the Invention

Cytokines belong to a large group of polypeptide- or glycopeptide-signaling molecules that act, at extremely low concentrations, as regulators of cell growth and essential mediators of inflammation and immune reactions. The production and functions of cytokines are tightly regulated by cytokines themselves and by several other factors. Most cytokines act locally and are implicated in a number of inflammatory conditions. These include rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease.

The antimalarial compounds chloroquine and hydroxychloroquine are known as broadly active, modestly potent inhibitors of cytokines. Such antimalarial agents have become important disease-modifying antirheumatic agents (DMARD) in the second line treatment of rheumatoid arthritis and other inflammatory disorders. Other agents in this class include gold, penicillamine, methotrexate and cyclosporins, all of which have potent activity. However, the utility of these latter drugs for the treatment of a chronic disease such as rheumatoid arthritis is limited by serious side-effects. The antimalarial agents in the DMARD class are recognised as having a more moderate side-effect profile, while possibly lacking the potency of some of the other agents. However, there is still concern about the ocular side-effects of both chloroquine and hydroxychloroquine. Thus, it may be postulated that a drug for the treatment of arthritis that possesses an improved efficacy versus side-effect profile over hydroxychloroquine, the most significant antimalarial drug in the DMARD class, would be of significant clinical potential.

In terms of antimalarial potency, mefloquine is one of the most effective drugs indicated for both prophylaxis and treatment and has particular utility for use in chloroquine-resistant malaria. Chloroquine has been the mainstay of antimalarial treatment and prophylaxis, but the emergence of chloroquine resistance in *Plasmodium falciparum*, the most lethal strain, has started to limit its utility. Thus mefloquine has emerged as the preferred compound for the prophylaxis and treatment of malignant malaria.

Mefloquine enantiomers have been evaluated in animal models for efficacy against *Plasmodium* species. These studies concluded that there was no difference in antimalarial potency of the enantiomers.

Summary of the Invention

Surprisingly, it has been found that (+)-mefloquine possesses potent anti-rheumatic properties. The use of the substantially pure enantiomer may maximise efficacy and reduce unwanted side-effects. (+)-*Erythro*-mefloquine is a more potent inhibitor of cytokines implicated in the inflammatory response. (+)-*Erythro*-mefloquine suppresses human lymphocyte proliferation.

Description of the Invention

The present invention is based, at least in part, on the finding that mefloquine shows a broad profile of cytokine inhibition, consistent with antimalarial RA therapy. In addition, it has been shown that the isomers of mefloquine show good activity against Interleukin-8 (IL-8). Both chloroquine and hydroxychloroquine are inactive against IL-8, and this cytokine is implicated in the progression of inflammation and tissue destruction inherent in the progress of RA and OA. This is a significant aspect of the enhanced profile of mefloquine isomers in the treatment of inflammatory conditions. In addition, as shown in Table 1, the isomers of mefloquine have superior activity over chloroquine and hydroxychloroquine against IL-2, a cytokine implicated in the destruction of connective tissue in RA and OA.

Table 1. Inhibition Profile (IC_{50}, μM)

	TNF	IL-1	IL-6	IL-8	IL-2	T-cell proliferation	IFN gamma
Hydroxychloroquine	32.2	21	90	Inactive	94	16	94
Chloroquine	21	6.3	81	Inactive	66	13	63
(-)Mefloquine	18	79	43	63	17	10	18
(+)Mefloquine	24	68	53	41	17	11	17

This inhibition profile has shown significant activity in a preclinical, *ex vivo* assay of tissue destruction in the bovine nasal cartilage model. The results are shown in Table 2.

Table 2. Inhibition of IL-2-stimulated bovine nasal cartilage destruction

	1μM	10μM	100μM
Hydroxychloroquine	4	3	36
Chloroquine	3	6	35
(+/-)Mefloquine		20	
(-)Mefloquine	37	45	82
(+)Mefloquine	32	44	71

For use in the invention, the active agent may be formulated, e.g. together with a carrier, excipient or diluent, and administered, by procedures that are known in the art, including those already proposed for the racemate. Suitable compositions will depend on the intended route of administration, which may be, for example, oral, topical, nasal, rectal, sublingual, buccal or transdermal. Sustained, delayed, timed or immediate release compositions may be used.

The amount of the agent that should be administered can readily be determined by the skilled man, taking into account the usual factors such as the type of patient, the nature of the condition being treated, and the route of administration. The amount of enantiomer may be higher or the same as that for the racemate, or may be modified depending on the co-administration of other drugs.

Conditions that may be treated include conditions involving cartilage destruction, inflammatory conditions and those mediated by IL-2 and IL-6, e.g. rheumatoid arthritis, asthma, psoriasis, psoriatic arthritis, Crohn's disease, irritable bowel syndrome and systemic lupus erythematosus. Other relevant conditions are ulcerative colitis, COPD and asthma. The patient may be disposed to CNS side-effects, and/or may be undergoing concomitant therapy with another drug.

Depending on the relative activities of the individual enantiomers, it may be preferred to administer a mixture, e.g. racemate, or substantially one enantiomer. The desired enantiomer may be in at least 50%, 70%, 90%, 95% or 99% excess, with respect to any other. The active agent may be used in any active form, e.g. salt or non-salt.

The use of (+)-erythro-mefloquine is preferred. It appears that this compound is particularly useful in providing the desired effect, without tissue destruction, and can be safely administered at a relatively high dosage.

CLAIMS

1. Use of mefloquine for the manufacture of a medicament for the treatment of an inflammatory disease or an autoimmune disease.

2. Use according to claim 1, wherein the mefloquine is in the form of (+)-*erythro*-mefloquine, substantially free of (-)-*erythro*-mefloquine.

3. Use according to claim 1 or claim 2, wherein the inflammatory disease is rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, Crohn's disease, systemic lupus erythematosus, ulcerative colitis, COPD or asthma.

4. A method of treating an inflammatory disease or an autoimmune disease in a subject, which comprises the administration of mefloquine to the subject.

5. A method according to claim 4, which comprises the administration of (+)-*erythro*-mefloquine, substantially free of (-)-*erythro*-mefloquine.

6. A method according to claim 4 or claim 5, wherein the inflammatory disease is rheumatoid arthritis, osteoarthritis, psoriatic arthritis, psoriasis, Crohn's disease, systemic lupus erythematosus, ulcerative colitis, COPD or asthma.

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(54) Title: THE TREATMENT OF INFLAMMATORY DISORDERS

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INTERNATIONAL SEARCH REPORT

Ir. ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/49 A61P19/00 A61P17/06 A61P1/00 A61P11/08
A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, BIOSIS, MEDLINE, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BATES, EDNA J. ET AL: "Stimulation of human neutrophil degranulation by mefloquine" INT. ARCH. ALLERGY APPL. IMMUNOL. (1988), 86(4), 446-52, XP000979855 abstract page 446, column 1, paragraph 1 page 450, column 2, paragraphs 4,5 --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAINSFORD K D: "EFFECTS OF ANTIMALARIAL DRUGS ON INTERLEUKIN 1-INDUCED CARTILAGE PROTEOGLYCAN DEGRADATION IN-VITRO" JOURNAL OF PHARMACY AND PHARMACOLOGY,GB,LONDON, vol. 38, no. 11, 1986, pages 829-833, XP000889827 ISSN: 0022-3573 abstract page 829, column 1, paragraph 1 ---	1,4
X	FONTAGNE, J. ET AL: "Effects of some antimalarial drugs on rat inflammatory polymorphonuclear leukocyte function" BIOMED. PHARMACOTHER. (1989), 43(1), 43-51, XP000981559 abstract page 44, column 1, paragraphs 1-3 page 50, column 2, paragraphs 2,3 ---	1,4
X,P	WO 00 66107 A (APT PHARMACEUTICALS L L C) 9 November 2000 (2000-11-09) abstract page 21, line 15-18 page 44, line 3-27; claims 1,29,32-39; examples 1-3 ---	1-6
X	WO 90 00055 A (DAVIS MICHAEL H) 11 January 1990 (1990-01-11) abstract page 3, paragraph 3 -page 4, paragraph 4 ---	1,4
X	DEAN GOLDRING J P ET AL: "Antimalarial drugs modulate the expression of monocyte receptors." INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, vol. 21, no. 9, 1999, pages 599-607, XP000979856 ISSN: 0192-0561 abstract -----	1,4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The terms "inflammatory disease or autoimmune disease" is not clear in the present context because the artisan skilled in the field of therapy can not enumerate exhaustively which disease is comprised within this term.
Claims searched completely: 3,6
Claims searched incompletely: 1,2,4,5

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/03924

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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